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Neonatal Abstinence Syndrome: An Update

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Abstract

Purpose of review—This review provides an update focused on the evolving epidemiology of neonatal abstinence syndrome (NAS), factors influencing disease expression, advances in clinical assessment of withdrawal, novel approaches to treat NAS, and the emerging role of quality improvement work in the field of NAS.

Recent Findings—The rise in the incidence of NAS disproportionately occurred in rural and suburban areas. Polysubstance exposure and genetic polymorphisms modified NAS expression and severity. Several centers have explored the use of new bedside assessments, focused on fewer factors to identify infants with NAS, that resulted in a decreased proportion of infants receiving pharmacotherapy for NAS. In addition, buprenorphine was shown to be a promising therapeutic alternative to morphine for treatment of NAS. Lastly, local, state and national quality improvement initiatives aimed to improve outcomes for infants with NAS emerged as an effective manner to advance the care of infants with NAS.

Summary—NAS remains a critical public health issue associated with significant medical, economic and personal burden. Emerging data on drivers of disease, assessment of withdrawal and treatment for NAS provide clinicians and hospitals with new knowledge and an urgency to promote standardization of care for infants with NAS.

Keywords

Neonatal abstinence syndrome; withdrawal; maternal drug use; non-pharmacologic treatment; buprenorphine

Introduction

Neonatal abstinence syndrome (NAS) is a postnatal drug withdrawal syndrome exhibited by some opioid-exposed infants that is characterized by hyperactivity of the central and

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autonomic nervous system and gastrointestinal tract. Over the last two decades, the US incidence of NAS has sharply increased from 1.19 per 1000 hospital births in 2000, to 5.63 in 2012. During the same time period, the number of infants treated for the syndrome in US neonatal intensive care units increased five-fold (1, 2). Although NAS has been described in the medical literature for several decades, (3) factors that modulate disease expression and severity remain poorly defined. As a result, clinical uncertainty exists about which opioid-exposed infant will develop withdrawal. Further, variation in health care settings and interventions used for treatment are widespread across the US (4-6). Given the significant health care utilization (2) and the tremendous economic burden (7)* associated with NAS, there is a need to understand better the factors that modify disease expression and describe best practices to identify and treat NAS. This review will address the changing epidemiology of NAS, factors that influence disease expression, strategies to identify and treat NAS, and emerging data on the importance of standardizing care for affected infants.

Changing Epidemiology

Opioids are the most common illicit substance for which pregnant women seek treatment (8). The recent rise of opioid use in pregnancy and NAS has disproportionately occurred in rural areas (9, 10)** Using administrative data from 2004 to 2013, Villapiano et al.(11)* found the incidence of NAS per 1000 hospital births increased from 1.2 to 7.5 among rural infants and from 1.4 to 4.8 among urban infants. The demographic differences between rural and urban areas is also apparent in state surveillance data. For example, in 2016 in Tennessee the rate of AS per 1,000 births was 26.2 in rural east Tennessee compared to 5.6 in the urban Nashville area (12)*.

In addition to urban-rural differences, NAS incidence differs substantially among states. Ko et al. (10)** detailed state-specific NAS incidence rates per 1,000 hospital births in 2013. They found NAS incidence of 0.7 in Hawaii contrasted by 33.4 in West Virginia. This striking difference has notable implications for the expected health care needs of a given population and may help focus primary prevention (e.g., limits to opioid prescribing) and treatment expansion efforts in areas most affected by this epidemic. In order to garner more timely data for NAS many states, including Florida, Georgia, Kentucky and Tennessee, made the syndrome a publicly reportable condition, allowing for improved public health surveillance and targeted response (10)**. In some states (e.g., Tennessee) web-based reporting portals, emerged as a tool to provide realtime data on NAS.

Polysubstance Exposure and Disease Severity

Predicting which opioid-exposed infants will manifest clinical signs of withdrawal is difficult. Recently, antenatal polysubstance exposure and genetic polymorphisms emerged as key factors that may affect an infant's risk developing NAS. Improved understanding of these factors may allow for stratification of infants into categories of risk that would enable individualized observation and treatment plans (13, 14).

Huybrechts et al. (15)** used a national sample of over 200,000 publically insured pregnant women to investigate the impact of *in utero* co-exposure to psychotropic medications and

opioids on the incidence and severity of neonatal drug withdrawal. They observed that the risk of neonatal abstinence syndrome increased 30-60% in with co-exposure to antidepressants, benzodiazepines, and gabapentin. In this report, co-exposure to atypical antipsychotics or non-benzodiazepine hypnotics (e.g., Zolpidem) did not significantly increase the risk of withdrawal. Because the rate of psychotropic medication use in women who use opioids is high, this work may have immediate clinical applicability.

In addition to high rates of psychotropic medication use among pregnant women, rates of marijuana use are also high. Marijuana is the most commonly used illicit drug in pregnancy (16) and the role of co-exposure on modifying NAS expression and severity is unclear. O'Connor et al. (17)* performed a retrospective study of nearly 200 maternal-infant dyads in which the mother was maintained on buprenorphine and had marijuana exposure during the third trimester. The likelihood of an infant requiring pharmacologic treatment for NAS (27.6% in marijuana-exposed vs 15.7% in non-marijuana-exposed infants, p=0.66) or duration of infant hospital stay (7.7 days in marijuana exposed vs 6.6 days in non-exposed infants, p=0.53) were not significantly associated with marijuana exposure.

Genetic Mediators of Disease Severity

In adults, single-nucleotide polymorphisms (SNPs) in the mu-opioid receptor (OPRM1), multidrug resistance (ABCB1) and catechol-o-methyltransferase (COMT) genes are associated with risk for opioid addiction. Similarly, among newborns one recent report found that OPRM1 and COMT SNPs were associated with prolonged hospital length of stay and treatment for NAS (18). In addition, a recent pilot study of 21 methadone exposed newborns and their mothers by Mactier et al. (19)* found that infants treated for NAS were significantly more likely to carry the homozygous allele of the CYP2B6 gene that encodes a cytochrome P450 mono-oxygenase enzyme and is present in 75% of the Caucasian population. Recent advances in understanding how genomic variation and differential antenatal exposures contribute to NAS risk and severity may lead to tailored approaches to infant treatment based upon individual risk profiles.

Clinical Prediction Tools for NAS

Identification of specific factors that lead to NAS enabled the development of clinical prediction tools for NAS. One example is a "symptoms only tool" created by Isemann et al. (20)* intended to predict the need for pharmacologic treatment for NAS within 2 days of birth. Based on data from a retrospective analysis of 264 infants with *in utero* exposure to opioids, the authors designed a clinical prediction tool based upon on three highly predictive symptoms associated with the need for pharmacotherapy to treat NAS: increased muscle tone, tremors when disturbed, and excoriation. The current American Academy of Pediatrics guideline recommends 3 days of observation for short-acting opioids and 5-7 days for longer acting opioids (6). NAS prediction tools, such as the one designed by Isemann et al. may expedite treatment decisions in at-risk infants and optimize health care utilization for those who are thought to be at low risk for developing withdrawal requiring pharmacotherapy.

Identification of NAS: What tool to use?

The approach to how and where in a hospital (e.g., newborn nursery, mother's room, NICU) infants are evaluated for signs of withdrawal is not standardized (21, 22). A modified version of the Finnegan Neonatal Abstinence Scoring System (FNASS) is the most commonly used tool to assess newborns for signs of withdrawal (21). The FNASS assigns a numerical score to 21 subjective clinical signs of NAS to determine NAS severity and is used to guide pharmacological treatment. Notably, the tool has not been validated to show utility in improving outcomes for infants with NAS (6). In an alternative approach that focused on a small number of clinically relevant factors, Grossman et al. (23)** describe novel criteria for the clinical assessment of infants with NAS, developed as part of a single center quality improvement project to improve care of substance exposed infants. This functional assessment used 3 parameters: the infant's ability to eat, to sleep, and to be consoled. If the infant was able to be breastfed or take >1 ounce from a bottle per feed, to sleep undisturbed for >1 hour, and could be consoled if crying within 10 minutes, pharmacologic treatment with morphine was not started or increased regardless of other signs of withdrawal. This intervention, along with others in the project, significantly reduced the proportion of methadone-exposed infants treated with morphine from 98% to 14%. Grossman et al. suggest that the FNASS guided approach to treating NAS encourages providers to treat a number and not a patient, and call for change in practice to the assessment of withdrawal signs (24)*. In another quality improvement effort, Holmes et al. describe a “infant-centered scoring” protocol in which the infants were scored only after on-demand feeds during skin-to-skin care (25)**. This modification aimed to avoid waking infants from sleep for scoring, removing them from family members’ arms to be assessed, and assigning points to infants for crying when hungry. Although these innovations await rigorous evaluation and validation, they demonstrate that QI methodology plays a promising role in reducing the number of infants exposed to opioid treatment for NAS.

Where to treat NAS

Newborn infants with NAS are treated and observed in a variety of hospital settings including newborn nursery, inpatient pediatric wards and neonatal intensive care units (NICU). Although NICU settings provide the highest level acute care, they may separate the dyad which creates barriers to breastfeeding and rooming in both of which may decrease length of treatment and hospital stay for NAS (26, 27). Holmes et al. demonstrated decreased hospital cost and length of stay for infants with NAS who experienced full rooming-in for observation and treatment on mother-infant pediatric units (25)**. Howard et al. (28)* retrospectively assessed the impact of parental presence at the bedside among 86 mother-infant pairs. They found in adjusted analysis that parental presence was significantly associated with 5.7 fewer days (p=0.03) of opioid therapy for NAS and a trend toward shorter LOS by >5 days (p =0.9). Additionally, maximal parental presence was associated with reduced opioid treatment days. These data suggest that strategies that promote rooming-in and minimize the separation of the maternal-infant dyad hold promise as non-pharmacologic treatment for NAS. When family or maternal presence is limited, programs using volunteers to provide comfort to infants with NAS may provide an alternative (25)**.

As hospital systems strategize where opioid exposed infants will be observed and treated, priority should be placed on keeping the maternal-infant dyad together.

Pharmacologic treatment of NAS

Infants with NAS are often treated pharmacologically and morphine is the most frequent opioid used to treat NAS (29). New evidence suggests that buprenorphine, a partial *mu* opioid receptor agonist and full *kappa* opioid receptor antagonist successfully used in adults to treat opioid withdrawal, may be a better alternative in infants.(30)**. In the Blinded Buprenorphine or Neonatal Morphine Solution (BBORN) trial, a single-site randomized double-masked, double-dummy trial, sublingual buprenorphine was compared to oral morphine in 63 infants with NAS. They found that both the median duration of treatment (15 days vs 28 days, difference 13 days, 95% CI 7-21 days; p <0.001) and the median length of hospital stay (21 vs 33 days, difference 12 days, 95% CI 7-22 days; p <0.002) were shorter in the buprenorphine vs morphine group. The number of infants who received supplemental phenobarbital as adjunct therapy and the rates of adverse events were not different between the groups. These results highlight a potential new therapeutic option for infants with NAS that may decrease exposure to opioids and health care utilization.

Standardizing initiation and weaning of pharmacotherapy for NAS

In addition to gaining a better understating of what medication is ideal when pharmacologic intervention is needed, working to standardize care across centers is of critical importance. The Vermont Oxford Network launched a two-year multicenter QI collaborative for infants with NAS by in 2012 that included 199 centers. The collaborative was formed in response to the American Academy of Pediatrics (AAP) policy statement released in 2012 calling for standardization of care delivered to infants with NAS (6). In a prospective cohort study utilizing serial cross-sectional audits of participating centers, Patrick *et al.* (29)* found that among participating centers, the mean number of NAS focused guidelines increased from 3.7 to 5.1 of a possible 6 (p <0.001) and among infants cared for at participating centers decreases occurred in both median length of pharmacologic treatment (16 to 15 days, p=0.02) and infant length of stay (21 days to 19 days, p=0.002).

In addition to increased standardization of initiation of pharmacotherapy for NAS, improved strategies to wean treatment are also needed. A multicenter retrospective cohort study from the Ohio NAS research collaborative focused on the implementation of a standardized NAS weaning protocol (31). From 2012 to 2014, 981 infants completed pharmacologic treatment for NAS with methadone or morphine in one of the six children's hospitals in Ohio. Half-way through the study period, all hospitals adopted strict guidelines for weaning opioids. At the three centers who did not previously have a guideline, the switch to a strict weaning guideline was associated with shorter duration of opioid treatment (23.0 *vs.* 34.0 days, P<0.001), shorter inpatient hospitalizations (23.7 *vs.* 31.6 days, P<0.001), and less adjunctive drug therapy (5% *vs.* 21%, P=0.004). This study highlights the benefits of a standardized weaning protocol and the role of statewide collaboration to optimize outcomes for infants with NAS.

Conclusion

The personal and societal burden of NAS continues to grow across the United States. Although understanding of the factors that influence disease severity have led to development of clinical prediction tools, more work is needed to discern the utility of such tools. A body of evidence has emerged describing new assessment techniques that prioritize a few functional infant symptoms to drive the need for treatment of NAS. If applied widely, these may drastically reduce the number of infants exposed to opioid treatment for NAS with subsequent reduction in health care utilization and cost. Further work is needed to identify if these modified tools can produce similar results across multiple centers. Additional research is necessary to identify the optimal medication, including dosing interval and indication for pharmacologic intervention. Lastly, state level data and national quality improvement data are needed to identify trends in real-time and drive policy interventions aimed to address this critical public health issue.

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Key Points

- Polysubstance exposure and specific genetic polymorphisms influence severity of NAS and should be considered when designing clinical prediction tools aimed at personalizing the care of infants with NAS.
- Utilizing modified tools, when observing opioid exposed infants for withdrawal, that focus on clinically relevant infant characteristics may drastically reduce the number of infants treated pharmacologically for NAS.
- Buprenorphine treatment for the pharmacologic management of NAS has been shown to decrease days of treatment and length of hospital stay, making it a promising new therapy for treatment of NAS.
- • State based data is key to identify the changing epidemiology of NAS and provides the necessary framework for policy, public health, and clinical interventions.